Seizure 23 (2014) 367–370

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

The usefulness of the head-up tilt test in patients with suspected epilepsy

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ARTICLE INFO

Article history:
Received 28 July 2013
Received in revised form 7 February 2014
Accepted 9 February 2014

Keywords:
Epilepsy
Misdiagnosis
Neurocardiogenic syncope
Head-up tilt test

ABSTRACT

Purpose: It is estimated that approximately 20–30% of patients diagnosed with epilepsy have been misdiagnosed, and neurocardiogenic syncope (NCS) might frequently be the real cause of transient loss of consciousness (TLOC) episodes.

We assessed the role of the head-up tilt test (HUTT) in patients previously diagnosed with refractory epilepsy to evaluate the ability of this test to correctly diagnose patients with NCS.

Method: We retrospectively analysed the clinical records of 107 consecutive patients with a previous diagnosis of refractory epilepsy that were taking antiepileptic drugs and who were referred for HUTT between January 2000 and December 2010. During the subsequent follow-up, we recorded the treatments performed and the recurrence of symptoms.

Results: Complete follow-up data were available for 94 (88%) patients, and the mean follow-up period was 80 ± 36 months. The HUTT was positive in 54% of patients. Thirty-one (33%) patients were misdiagnosed with epilepsy, and 20 (21%) patients had a dual diagnosis of NCS and epilepsy. The recurrence of TLOC was reported in 55% of the patients, but it was significantly lower in the misdiagnosed group (42% versus 64%; $P = 0.039$).

Conclusion: NCS is an important cause of epilepsy misdiagnosis. The HUTT is often critical for making an accurate diagnosis and subsequently selecting the appropriate treatment for patients presenting with TLOC. The diagnostic overlap between epilepsy and NCS is not uncommon, suggesting that electroencephalographic monitoring during a HUTT may play an important role in diagnosing patients with recurrent, undiagnosed TLOC episodes.

1. Introduction

Epilepsy and syncope, two prevalent clinical conditions, are frequently initially diagnosed incorrectly.[1,2] Transient loss of consciousness (TLOC) associated with involuntary motor activity is sometimes mistaken for epilepsy and, consequently, antiepileptic drugs (AEDs) are often prescribed in these circumstances.[3,4] It is estimated that 20–30% of patients diagnosed with epilepsy have been misdiagnosed, and neurocardiogenic syncope (NCS) might be the most frequent cause of this mistake.[4,5] An incorrect diagnosis of epilepsy can lead to inadequate therapeutic treatments and prognostic deductions, which can subsequently cause refractory therapy, adverse secondary effects of the AED, symptom recurrence, and a delayed identification of the real TLOC cause.

When differentiating between syncope and epilepsy, it is extremely helpful to carefully and methodically analyse the patient's history.[6] However, a complete and accurate history may not be sufficient to differentiate between the two clinical entities, and the head-up tilt test (HUTT) has already proven to be a valuable diagnostic tool when investigating unexplained TLOC.[7] Nonetheless, it is not well established how prevalent a dual diagnosis of NCS and epilepsy is or how a systematic performance of the HUTT and an electroencephalogram (EEG) test in patients with TLOC might help to achieve a more accurate diagnosis. In patients with refractory TLOC, we aimed to assess the role of the

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http://dx.doi.org/10.1016/j.seizure.2014.02.004
1059-1311/

HUTT in the diagnosis of NCS, the prevalence of a dual diagnosis of NCS and epilepsy, and the frequency of symptom recurrence in a long-term follow-up for each group.

2. Methods

In this study, we retrospectively analysed the clinical records of 107 patients with a prior diagnosis of refractory epilepsy that were taking AEDs and who were consecutively referred to an Autonomic Clinic for HUTT between January 2000 and December 2010. Exclusion criteria included patients without an available EEG.

Refractory epilepsy was defined as a failure to achieve a sustained absence of seizures following two trials of tolerated and appropriately chosen AED regimens of either mono- or combination therapy.[8] The diagnosis of refractory epilepsy was established by the patient's neurologist and was based on symptom recurrence, which was occasionally associated with dubious clinical manifestations. The epileptiform activity on EEGs was defined as characteristic waves or wave complexes, distinct from the background activity, and resembling those recorded in a group of human subjects suffering from epileptic disorders.[9]

When the patients underwent the HUTT, they completed a questionnaire to obtain clinical details including pre- and post-TLOC symptoms. The HUTT was performed according to the guidelines of the European Society of Cardiology, which involves a 70° upright head-up tilt in an electric tilt table with footplate support and body straps for up to 40 min. Blood pressure was monitored using digital photoplethysmography (Finapres®), and an electrocardiogram was continuously recorded throughout the study. When no syncopal event was observed during the tilting phase (baseline), sublingual nitrates were administered. Patients over 40 years of age were also examined with bilateral carotid massage, which was performed in the supine position and after a prolonged orthostasis whenever there was no contraindication. A positive HUTT required the presence of syncope or pre-syncope, associated with the reproduction of usual clinical symptoms, and a significant sudden drop in blood pressure and/or heart rate.

A final clinical diagnosis was supported by a consensus between a neurologist and a cardiologist and was based on the patient's clinical features and the results of the HUTT and the EEG (Table 1):

- Epilepsy alone: negative HUTT and symptoms and EEG consistent with epilepsy.
- NCS alone: typical clinical reproduction of symptoms during the HUTT and symptoms and EEG not consistent with epilepsy.
- Dual diagnosis of epilepsy and NCS: typical clinical reproduction during the HUTT of some of the patients' symptoms, but coexistence of other episodes, symptoms and EEG consistent with epilepsy.
- TLOC of unknown cause: unspecific symptoms, negative HUTT and EEG not consistent with epilepsy.

The patients' subsequent follow-up was performed via a telephone interview to evaluate their clinical evolution, including treatments performed and symptom recurrence. Clinical records for each patient were carefully reviewed to complete the information regarding symptom recurrence as well as type and date of clinical outcomes. We considered clinical outcome a recurrence of sudden spontaneous TLOC, which presented with the same characteristics of the previous episodes.

2.1. Statistical analysis

We calculated the mean of continuous variables and the frequency of categorical variables. Comparisons were made using ANOVA (Scheffe's F test) for continuous variables, and the chi-square test was used for categorical variables. The cumulative proportion of TLOC recurrence was estimated via the Kaplan–Meier method by plotting proportion recurrences as a function of time. The survival curves according to the final diagnosis (NCS versus epilepsy/dual diagnosis) were compared using the log-rank test. Two-tailed P-values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS Statistics version 19.0 (SPSS Inc., Chicago, IL).

Table 1
Clinical characteristics according to final clinical diagnosis.

Variables	Total (N = 94; 100%)	Epilepsy (N = 39; 41%)	NCS (N = 31; 29%)	Dual (N = 20; 21%)	P value
Age (years), mean (SD)	39 (17)	40 (15)	33 (16)	41 (18)	0.160
Female, N (%)	67 (71)	27 (69)	22 (71)	15 (75)	0.898
Episode frequency					
Weekly	3 (3)	2 (5)	1 (3)	0 (0)	0.457
Monthly	28 (30)	14 (36)	7 (23)	5 (25)	
Bi-annually	31 (33)	9 (23)	14 (45)	7 (35)	
Annually	32 (34)	14 (36)	9 (29)	8 (40)	
Prodromal/associated signs and symptoms					
Visual symptoms	50 (53)	21 (54)	18 (58)	9 (45)	0.657
Dizziness and light-headedness	62 (66)	26 (67)	21 (68)	12 (60)	0.835
Diaphoresis	34 (36)	13 (33)	13 (42)	8 (40)	0.742
Palpitations	33 (35)	17 (44)	7 (23)	7 (35)	0.185
Nausea/vomiting	17 (18)	8 (21)	7 (23)	2 (10)	0.198
Pallor	33 (35)	13 (33)	11 (35)	7 (35)	0.981
Asthenia	49 (52)	22 (56)	17 (55)	9 (45)	0.693
Myoclonic movements	71 (76)	34 (87)	22 (71)	15 (75)	0.098
Sphincter incontinence	18 (19)	12 (31)	3 (10)	3 (15)	0.074
History of trauma	32 (34)	19 (49)	7 (23)	6 (30)	0.064
Precipitated by standing position	59 (63)	20 (52)	23 (74)	14 (70)	0.111
Comorbidities					
Hypertension	10 (11)	3 (8)	4 (13)	2 (10)	0.253
Diabetes mellitus	4 (4)	1 (3)	0 (0)	2 (10)	0.142
Cardiac disease	2 (2)	2 (5)	0 (0)	0 (0)	0.516
Psychiatric disease	4 (4)	2 (5)	0 (0)	0 (0)	0.920

* Statistical significance for p value < 0.05.

3. Results

Of the nearly 3800 patients that had a HUTT performed between 2000 and 2010, 174 patients (4.6%) were diagnosed with "refractory epilepsy" and were taking AEDs. Of these, 107 patients with at least one EEG available were included in the study population. The study population consisted of 68% females and an overall mean age of 38 ± 17 years. Only 3% of the patients reported frequent (weekly) episodes of TLOC. Regarding prodromal or associated features, 86% of the patients reported limb movements, 19% reported sphincter incontinence and 63% mentioned episode occurrence in the standing position. Trauma was also relatively frequent (34%) in this patient population.

An inadequate or missing history (no witness and/or poor description regarding associated symptoms) was present in 23% of the study population. Doubts regarding the accuracy of the previously established diagnosis (epilepsy) were the most common reason (91%) of referral for HUTT. Some patients (9%) were also referred for HUTT due to the clinician's suspicion of a dual diagnosis of epilepsy and NCS.

Follow-up data were available for 94 (88%) patients, with a mean follow-up period of 80 ± 36 months. These patients presented a mean age of 39 ± 17 years, and 67 (71%) patients were women. Fifty-one patients (54%) experienced their usual symptoms during the HUTT, which were associated with profound hypotension and/or bradycardia that is consistent with a clinical diagnosis of NCS (vasodepressor response in 57%, cardioinhibitory in 6%, and mixed in 37%).

The final clinical diagnostic groups and patients' main clinical characteristics are presented in Table 1. Forty-one percent of patients were classified as having only epilepsy, 33% were classified as having only NCS, 21% were classified as having a dual diagnosis of epilepsy and NCS, and 4% of the patients were unable to be classified as having epilepsy or NCS.

No significant differences were found between the final diagnostic groups regarding anthropometric features, symptom characteristics and comorbidities. There were no significant differences in the type of HUTT response between the misdiagnosed group and the dual diagnosis group ($P > 0.05$).

Carotid sinus syndrome was not present in this study population.

All misdiagnosed patients stopped taking AEDs. Most of the misdiagnosed patients were advised to increase salt and water intake and perform physical counter pressure manoeuvres, while some patients (15%) received new pharmacological treatments (Midodrine and/or a beta-blocker).

3.1. TLOC recurrence

TLOC recurrence was reported in 55% of the patients (Table 2) and recurrence was significantly lower in the misdiagnosed group of patients compared with the rest of the patient population (42% versus 64%; $P = 0.039$). A tendency towards a lower rate of symptom recurrence was observed in positive versus negative HUTT groups (49% versus 69%, respectively; $P = 0.066$).

Table 2
Syncope recurrence during the follow-up according to final clinical diagnosis.

Diagnosis	Patients, *N* (%)	Symptom recurrence, *N* (%)
NCS	31 (33)	13 (42)
NCS + epilepsy	20 (21)	12 (60)
Epilepsy	39 (41)	24 (62)
Unknown cause	4 (4)	3 (75)
Total	94 (100)	52 (55)

NCS, neurocardiogenic syncope.

The survival curves obtained for the groups based on final diagnosis (NCS alone versus dual diagnosis) are shown in Fig. 1. A significant difference regarding TLOC recurrence was observed in patients with misdiagnosed epilepsy compared with the rest of the patient population (log-rank test: $P = 0.009$). The mean time for diagnosing TLOC recurrence in the misdiagnosed branch (NCS alone) was 19 ± 11 months compared to 10 ± 7 months in the epilepsy/dual diagnosis branch.

In the follow-up evaluation, none of the NCS patients had their diagnosis changed to epilepsy.

4. Discussion

In this study, we addressed the usefulness of HUTT in patients diagnosed with epilepsy. Here, we reported a significant percentage (33%) of patients who were misdiagnosed and had a final diagnosis of NCS. Additionally, a dual diagnosis of NCS and epilepsy was also frequently observed (21%). Interestingly, upon follow-up, we found high rates of TLOC recurrence, in both patients with a final diagnosis of NCS and epilepsy, although the recurrence was higher in the epilepsy group.

The difficulty in distinguishing epilepsy from NCS has long been recognised.[3] Although a detailed history and witness account are essential for an accurate diagnosis, this may not be enough to differentiate between the two clinical entities. Contributing factors for misdiagnosing epilepsy are brief jerking or urinary incontinence associated with TLOC, a family history of epilepsy, and overvalorisation of minor abnormalities or normal-age specific variants on EEGs.

The HUTT is an important tool for detecting NCS in patients with TLOC of unknown aetiology. The HUTT test is safe, well tolerated, and presents adequate sensitivity, specificity and reproducibility, especially when symptoms are reproduced during the test.[7,10] This study included patients who were referred for the HUTT to reassess whether the TLOC episodes were related to a NCS instead of epilepsy (for example, due to a poor response to AEDs or

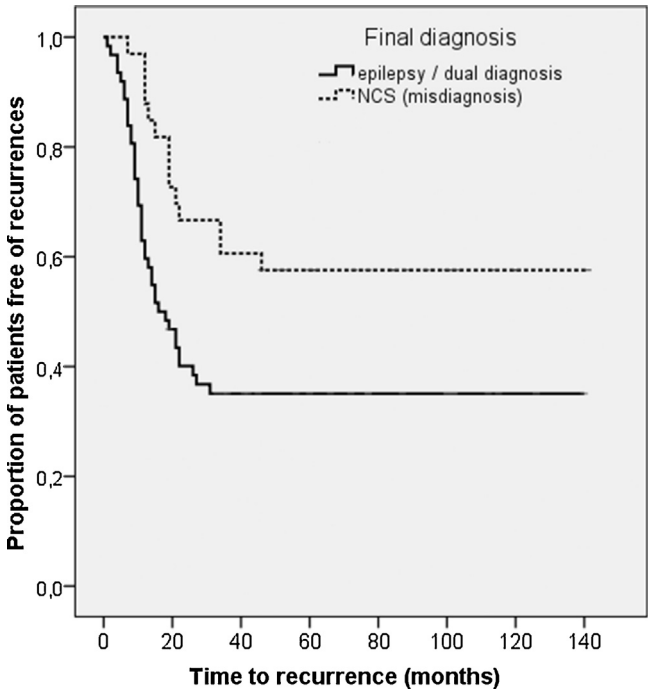

Fig. 1. Kaplan–Meier survival curves for TLOC recurrence according to the final clinical diagnosis: NCS (dashed line) and epilepsy ± NCS (continuous line). The *x*-axis shows months to the diagnosis of TLOC recurrence; the *y*-axis shows the proportion of subjects remaining TLOC-free. NCS, neurocardiogenic syncope.

to atypical premonitory symptoms in patients with initial epilepsy diagnosis). Our data showed that the HUTT is a simple, non-invasive tool that has an important role in confirming or refuting a diagnosis of NCS in patients with misdiagnosed epilepsy. Accordingly, this test led to a change in the diagnosis of approximately one-third of our patients.

It is essential to distinguish NCS from epilepsy because of differences in prognosis and treatment. Dealing with this type of syncope involves reassuring and counselling the patients on several aspects, such as avoiding precipitating factors and performing postural and counter pressure manoeuvres that can abort TLOC when patients feel pre-syncopal symptoms.

NCS is a common symptom in the general population and has a high recurrence rate.[11] Although there is little mortality associated with NCS, recurrent events can severely disable and may significantly influence the patient's overall quality of life.[12] In this study, more than 40% of patients with a final diagnosis of NCS continued to faint. Nevertheless, it must be emphasised that this study focused on a highly symptomatic cohort because the patients were selected based on recurrent events. Although some pharmacologic and non-pharmacological therapies may be beneficial to NCS patients, these therapies may be insufficient to prevent all recurrent episodes during a long follow-up period.[13] To the best of our knowledge, this is the longest follow-up study to evaluate the usefulness of HUTT in patients with suspected refractory epilepsy. Interestingly, none of the patients initially diagnosed with NCS had a diagnosis of epilepsy during the follow-up period, supporting the importance of HUTT in the diagnosis and differential diagnosis of NCS.

In cases involving a clinical suspicion of NCS, an EEG should not be requested because it would most likely not show specific epileptiform discharges. Instead, an EEG would show only normal phenomena or minor non-specific abnormalities that might lead to misleading reports and inappropriately prescribing AEDs.[14]

There was no cardiac (arrhythmic) syncope diagnosis because patients who were suspected of having this diagnosis were first observed by a cardiologist and only referred for the HUTT when that suspicion was refuted following a full evaluation.

An incorrect diagnosis of epilepsy can also arise from psychogenic non-epileptic seizures (PNES), which may occur in up to 12% of cases.[1] We reported four patients that had both their epilepsy and NCS diagnoses refuted and whose TLOC aetiology was still under investigation. It is possible that the patients with TLOC of unknown aetiology were suffering from PNES.

The misdiagnosis of epilepsy may bring significant clinical, psychosocial and socioeconomic problems to the patient. Patients may present AED intolerance, dose-related neurotoxicity and acute allergic reactions, among other significant side effects. It is important to emphasise that a misdiagnosis naturally delays the diagnosis of the real cause of TLOC. Additionally, it should be mentioned that it might be complicated to overcome the negative social consequences of a misdiagnosis of epilepsy.[14]

Additionally, there are considerable costs associated with an incorrect diagnosis of drug-resistant epilepsy.[15]

A dual diagnosis of NCS and epilepsy following a HUTT evaluation has been previously reported in one-third of patients having a final diagnosis of epilepsy.[16] In our study, roughly one-fifth of the total TLOC population was diagnosed with both NCS and epilepsy.

The key element in NCS is transient global cerebral ischaemia secondary to severe hypotension, bradycardia, or both. Studies have shown that electroencephalographic characteristics related to the NCS (due to the transient cerebral anoxia) are quite distinctive from those associated with epilepsy. In patients with reflex syncope, EEG monitoring during the HUTT could provide valuable data to support the interpretation of seizure-like episodes. In patients who presented with myoclonic jerky movements during a HUTT-induced syncope, EEG was useful for demonstrating how the theta and delta waves slowed without a spike or spike-wave activity.[17] Therefore, we believe that electroencephalographic monitoring during the HUTT could have an important role in obtaining the most accurate diagnosis for patients with recurrent non-diagnosed TLOC.

The retrospective and single centre, non-randomised nature of this study may present limitations for our results. Only patients referred for the HUTT were selected to participate in this study, and we could not control the selection criteria for this referral. Additionally, we did not perform an EEG during the HUTT.

5. Conclusion

The NCS is an important frequent cause of misdiagnosed epilepsy. The HUTT is crucial for obtaining an accurate diagnosis and to select the appropriate treatment for patients with TLOC to reduce its recurrence. A diagnostic overlap of epilepsy and NCS is not uncommon, suggesting that electroencephalographic monitoring during the HUTT may play an important role in patients manifesting with recurrent undiagnosed blackouts.

Conflict of interest statement

None of the authors have any conflicts of interest to disclose.

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